Fibroblast Growth Factor 23:
A Novel Key to Find Hidden Substrates of Atrial Fibrillation?

Running title: Kalyanasundaram et al.; FGF 23 and Atrial Fibrillation risk

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Cardiovascular disease (CVD) and the associated rhythm abnormalities manifesting as tachyarrhythmias such as Atrial fibrillation (AF) continue as leading causes of morbidity and mortality in the United States and developed countries. In spite of the exciting momentum of new discoveries which have greatly improved our understanding of several key molecular mechanisms underlying AF, identifying and managing AF during its early onset stage is extremely challenging. Traditionally, direct causes for CVD have been attributed primarily to genes, ischemic heart disease, poor dietary choices and lack of exercise; studies later revealed that diseases such as high blood pressure, diabetes, obesity and chronic kidney disease (CKD) are powerful risk factors that can equally impact the heart and cause pathological structural remodeling, contractile dysfunction, hypertrophy and heart failure (HF) which are well established substrates for AF.

Of these, CKD has emerged as one of the most potent risk factors for developing CVD and particularly AF. In fact, the high rates of mortality reported in CKD patients are mainly due to cardiovascular complications including uremic cardiomyopathy and/or vascular calcifications leading to cardiac complications. Although the reciprocal cross-talk between dysfunctions of kidney and heart is well-known, very few common mechanisms have been conclusively identified that could be targeted to impact both CKD as well as CVD. In this context, Fibroblast Growth Factor 23 (FGF23), a recently described phosphate regulating hormone secreted by osteocytes and osteoblasts draws attention. FGF23 works via FGF receptors and/or specialized Klotho receptors to reduce gastrointestinal phosphate absorption and stimulate renal phosphate elimination. Its expression is positively linked to CKD, wherein FGF23 levels increase during the early stages of CKD and believed to play a role in increasing urinary phosphate excretion. Elevated FGF23 levels are also associated with progression of kidney disease and end stage renal...
failure as well as vascular calcifications and increased ventricular mass\(^4\). Thus, FGF23 has emerged in the recent years as a dependable serum bio-marker of early alterations in phosphate and bone metabolism indicating decreasing and/or worsening kidney function in CKD patients\(^4\).

The current dilemma is to determine if the increased FGF23 expression by itself can cause any of the associated “off-target” dysfunctions, mainly CVD\(^7\). Although several clinical studies have reported positive, dose dependent correlations between FGF23 expression and CVD, other than ventricular hypertrophy, a direct mechanistic effect of FGF23 on other aspects of cardiac dysfunction, specifically AF, is yet to be identified. Seiler et al\(^7\) have shown that FGF23 levels are associated with left-ventricular function and AF even in the absence of renal function impairment implicating a broader role for FGF23 in CVD and AF. However, it’s unclear whether FGF-23 acts directly on the myocardium to cause AF. At this juncture, in this issue of *Circulation*, Mathew et al\(^8\) have presented data from two large community based cohorts, the Multi-Ethnic Study of atherosclerosis (MESA) and the Cardiovascular Health Study (CHS) to implicate FGF23 in incident AF. This report presents a direct correlation between increased FGF23 levels and the incidence of AF thereby implicating altered mineral imbalance and kidney dysfunction in creating a susceptibility to AF. A major strength of this study is that the associations were detected in patients with no previous CVD which indicates that FGF23 levels could be a novel marker for abnormal mineral metabolism (a risk factor for CVD), even in the absence of other known CKD markers such as eGFR and urine ACR as well as heart failure symptoms. Moreover, they also show that new-onset AF is correlated with increasing FGF23 levels in populations without previous CVD implicating a temporal relationship between AF and higher FGF23 expression. This finding could have significant diagnostic value for early prediction of AF risk. As in most cases of AF, arrhythmogenic substrates remain undetected due
to the limitations of currently available diagnostic testing options\textsuperscript{9}. Based on the data presented by Mathew et al\textsuperscript{8}, increasing FGF23 levels could potentially indicate a \textit{critical window} within the temporal course of incident AF that could be clinically valuable to begin treatment options to specifically prevent development of AF substrate.

These findings also present novel directions to better understand FGF23 biology and its role in AF. Although several causal mechanisms have been shown to underlie AF pathology\textsuperscript{2} including, autonomic imbalance, cardiac ion channels, up- or down-regulation of gap junctions and autonomic receptor proteins and intracellular calcium cycling, pathological fibrotic remodeling of the atrial myocardium and associated conduction abnormalities are the leading causes of worsening prognosis for AF patients\textsuperscript{2, 9}. Mathew et al’s study also shows a strong association between higher FGF-23 and NT pro-BNP, a sensitive marker for myocardial wall tension and hemodynamic stress which are in turn associated with incident AF\textsuperscript{8}. Although the authors could not directly show evidence for arrhythmogenic atrial myocardial fibrosis, such pathological remodeling of the atria can develop in parallel to the observed increase in ventricular mass. In the light of all the available data that implicate FGF23 in AF etiology, it would be important to determine if FGF23 affects the structure and/or function of the atrium either directly or secondary to ventricular remodeling in order to establish this intriguing bone hormone in arrhythmogenesis.

The most convincing data linking FGF23 to ventricular hypertrophy comes from mouse models of CKD which have shown a direct role for FGF23 in causing cardiac hypertrophy\textsuperscript{10}. Although several mechanisms can be assigned to induce cardiac hypertrophy, altered calcium ($\text{Ca}^{2+}$) cycling within the cardiomyocyte has been well documented to play a causal role in triggered arrhythmias (especially AF) as well as cardiac hypertrophy and HF\textsuperscript{11}. Interestingly, a
recent study indicates that FGF23 can also contribute to altered intracellular Ca\textsuperscript{2+} dynamics which affect contractility as well as induce cardiac hypertrophy\textsuperscript{12} thereby presenting a novel mechanism by which FGF23 can be arrhythmogenic either by directly modifying calcium cycling or by creating substrates via structural remodeling that can facilitate AF. These are very attractive hypotheses that can potentially identify new mechanisms to explain the connection between FGF23 and rhythm abnormalities associated with CVD. However, they need to be further tested particularly in the known animal models of altered FGF23 signaling in order to target specific molecular mechanisms involved in FGF23 associated AF and to corroborate them with findings from large community wide clinical studies. More importantly, the role of FGF23 in developing a structural and functional AF substrate has to be established specifically in the human atrial myocardium to substantiate future studies as well as to design treatment options via its signaling pathway; one option is to use explanted human atrial tissue, both with and without structural heart disease, first to determine the presence of specific receptors to FGF23 and if activation of the cardiac specific FGF23 signaling in the heart has a direct role in development of AF. These studies can specifically identify the causal role of FGF23 in facilitating AF via structural substrates and/or cellular mechanisms of AF. Moreover, other vascular impairments including calcifications subsequent to the abnormal mineral metabolism associated with FGF23 cannot be discounted to play additive roles in promoting AF, secondary to direct effects on the heart.

One of the fascinating aspects of FGF23 function is its role in the complex Mineral-Bone Disorder (MBD) characteristic of chronic CKD, wherein FGF23 levels fluctuate positively with the parathyroid hormone as well as with phosphate levels but tend to be negatively correlated with 1,25-dihydroxyvitamin D (1,25(OH)\textsubscript{2}D, the active Vitamin D hormone), estimated...
glomerular filtration rate and tubular phosphate re-absorption\textsuperscript{13,14}. Of these, Vitamin D via it’s receptor has been shown to reduce blood pressure as well as adverse cardiac remodeling including myocardial fibrosis and left ventricular diastolic dysfunction in an experimental animal model of pressure overload\textsuperscript{15}. In the light of these findings, increased FGF23 could hypothetically influence cardiac remodeling and increase blood pressure by decreasing Vitamin D levels which could in turn form vulnerable substrates for AF development. The data also implicate the Vitamin D pathway as a potential mechanism for AF progression secondary to FGF23 elevation which definitely warrants further investigation, potentially in existing mouse models of altered Vitamin D pathway. These studies may determine if restoring Vitamin D levels in patients with elevated FGF23 levels can circumvent the deleterious effects of high FGF23\textsuperscript{14} and decrease the incidence of AF.

The current study by Mathew et al\textsuperscript{8} and previously available data, both from basic and clinical studies, conclusively show that FGF23 plays a role in both CKD and CVD via a renal-mineral metabolism axis that could play an important part in either causing or worsening AF. However, the details of this complicated interplay within and between multi-organs spanning the bone-mineral-kidney-heart axis is far from clear; especially, the source and direction of dysfunction in a complicated disease setting such as mineral imbalance and its broad range effects is quite challenging to decipher. Despite all the existing data, the fundamental question as to whether FGF23 directly causes any of the implicated disorders including kidney malfunction, bone-mineral imbalances, CVD and AF or is a beneficial compensatory response that is secondarily recruited to play catalytic roles in other pathways (e.g. Vitamin D metabolism) known to directly affect cardiac structure and function is yet to be determined. Mathew et al\textsuperscript{8} have quite clearly delineated a strong association between rising FGF23 levels and incident AF,
thereby emphasizing its importance as a potential pathway that could be utilized as a novel risk factor for AF. Future investigations should focus on understanding the fundamental role it plays in the heart in order to identify its true contribution to AF development.

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**References:**


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